REMARKS

In the Office Action dated May 5, 2006, the Examiner: (1) rejects claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶ 2 as being indefinite; (2) rejects claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1 as failing to comply with the enablement requirement; and (3) rejects claims 1 – 6, 8, 19 and 21 – 37 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement. Applicants respond to the rejections as follows:

Response to Rejection of Claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶2

The Examiner rejects claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶2 as being indefinite. With respect to claim 2, the Examiner states that the phrase "(b) of claim 1 further comprises" renders that claim and the claims that depend on it vague and indefinite because it is unclear whether the method of claim 2 is performed in addition to the step recited in claim 1. Applicants have amended claim 2 to clarify that the application of the formulas are how step (b) of claim 1 is accomplished and submit that this amendment overcomes the outstanding rejection. Support for this amendment may be found in the claim itself, as well as on page 24, line 12 – page 26, line 2 and page 28, line 11 – page 30, line 15 of the specification as filed. No new matter has been added. Because claims 3 – 5 depend on claim 2, Applicants submit that the rejection has been overcome with respect to those claims as well.

With respect to claim 19, the Examiner argues that the claim is indefinite because only the number of bases in the sense strand is recited. Applicants respectfully disagree with the Examiner, but in the interest of furthering prosecution have amended claim 19 to recite that there is also an antisense strand of 18 – 25 bases. Support for this amendment may, for example, be found on page 48, lines 12 – 16 and 27 – 29 of the application as filed. No new matter has been added. In light of this amendment, Applicants submit that the rejection has been overcome.

Applicants have amended claims 2 and 19 in a manner that they believe places the claims in condition for allowance, and if not allowed, in better condition for appeal. Applicants submit that the amendments are in compliance with 37 C.F.R. § 1.116 ("Amendments presenting rejected claims in better condition for appeal may be admitted.") and MPEP 714.12 ("Any amendment that will place the application either in condition for allowance or in better form for appeal may be entered."), because the amendments specifically take into account the Examiner's suggestions and "require only a cursory review by the examiner." MPEP 714.13.

Response to Rejections of Claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1

The Examiner rejects claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1 for allegedly failing to comply with the enablement requirement. Applicants respectfully submit that the Examiner's rejection is an inappropriate application of the enablement requirement. The enablement requirement is met if the description "'enables any mode of making and using the invention.'" *Johns Hopkins v. CellPro.* 152 F.3d 1342, 1361 (Fed. Cir. 1998) (quoting *Engel Indus., Inc. v. Lockformer Co.,* 946 F.2d 1528, 1533 (Fed. Cir. 1991)). Example V shows selection of siRNA with an increased likelihood of functionality using Formula VIII. This formula contains non-target specific criteria within claim one. Example VI further shows the selection of other rationally designed siRNA using the disclosed formulas of the present invention and thus demonstrates for example, how to practice claim 2. These examples, as well as other portions of the specification enable the rejected claims.

Applicants note that the Examiner has not shown what if any experimentation is necessary to practice the claims as amended. Instead, the Examiner appears to take issue with whether applying the claims over their breadth would allow for the selection of siRNA of a specific functionality. However, this position does not focus on the invention as claimed (in any but a few of the dependent claims) and fails to demonstrate that a person of ordinary skill in the art could not practice the invention.

Before turning to the specific issues raised by the Examiner, Applicants submit that distinguishing a few concepts may be advantageous. First, a "rationally designed siRNA" is an siRNA that has been selected by at least one non-target specific criterion that increases or decreases the likelihood of functionality. Thus, it is selected by at least one criterion other than the degree of complementarity or homology with a target sequence. As the specification notes, examples of these criterion include GC content, Tm, the number of times that a nucleotide repeats four or more times in a row, and the presence or absence of a particular base at at least one of sequence positions 1 – 19. A rationally designed siRNA in its broadest sense could in theory have any degree of absolute functionality. The limitation of claim 1 is that the criteria on which the siRNA is selected is the presence or absence of a particular base at at least one of sequence positions 1 – 19.

The "functionality" of an siRNA refers to the amount of silencing that the siRNA performs in a given system. Prior to Applicants' invention, in order to discern more functional from less function siRNA, persons of ordinary skill typically only had trial and error methods at their disposal. These efforts could of course identify the more highly functional siRNAs without implicating rational design, but they also could be undesirably time-consuming.

Applicants were the first to appreciate that the rational design criterion of the presence or absence of a particular base at at least one of sequence positions 1 – 19 could be used to increase or decrease the likelihood that a particular siRNA would be functional. Any one criterion (*e.g.* the presence or absence of a particular base at position 3 or 11) could be used, and the more that are used, the more reliable the predicted result will be.

This type of invention -- being able to increase the likelihood of an event -- has been deemed to merit patent protection in a number of other instances. *See e.g.,* U.S. Patent No. 7,070,929, *Genetic Markers for Improved Disease Resistance in Animals*

(BPI), claim 1 "wherein the presence of a G at nucleotide position 103 indicates that said pig has increased likelihood of . . ."; U.S. Patent No. 7,045,292, *Method and Marker for Identification of Pre-Malignancy and Malignancy and Therapeutic Intervention,* claim 1 "wherein aberrant extrachromosal gene amplification of cyclin D2 indicates an increased likelihood. . ." (A copy of the first pages of these patents and the claims are attached as exhibits 1 and 2 respectively.) Thus, because "anything under the sun" that is made by a person is patentable, *Diamond v. Chakrabarty,* 447 U.S. 303, 309 (1980), an enablement rejection cannot be based on an assertion that certain applications of a claim does not yield a functional siRNA.

Further it is unclear why the Examiner thinks that a person of ordinary skill could not take for example criterion A_3, look at a printout of the potential siRNA for a target and select an siRNA that satisfies the criterion (claim 1). There would be no guarantee that the selected siRNA would be functional, but it would have an increased likelihood of being functional as opposed to a random selection of a siRNA. Similarly, the Examiner has not demonstrated why a person of ordinary skill in the art could not score two siRNA according to Formula IX and select the one with the higher score (claim 2).

Applicants now turn to the Examiner's reasons for maintaining the rejection based on an alleged failure to comply with the enablement requirement.

First, on the bottom of page 3, the Examiner notes that claim 1 does not require the application of non-target specific criterion to at least two candidate siRNAs and implies that this renders the claim invalid. Applicants agree that claim 1 does not require the application of the criterion to at least two candidate siRNAs. But Applicants submit that this does not render the claim invalid.

Claim 1 is directed to selecting a rationally designed siRNA by applying at least one non-target specific criterion to at least one candidate siRNA and selecting that candidate siRNA if it satisfies the criterion. Examples of non-target specific criterion are presented throughout the specification, including but not limited to on page 21, line 32 –

page 22, line 10. In the most simplest application, a person of ordinary skill could as noted above list all of the potential siRNA that contain sense sequences that are the same as a region of a target and look for one that has, for example, the base A at position 3 on the sense strand. This siRNA would have an increased likelihood of being functional relative to the set of all possible siRNA that have antisense strands that are complementary to a given target.

Applicants respectfully submit that the Examiner has not shown that any level of experimentation is necessary to practice the steps of claim 1 or why a person of ordinary skill could not make and/or use the invention. Accordingly, Applicants request that the Examiner identify the specific step of claim 1 that a person of ordinary skill would not be able to make or use.

Second, on page 4 the Examiner asks Applicants to address the statement on page 26, lines 18 –29 in light of her interpretation that the specification suggests that the criteria in claims 2 and 19 are not proven and that a person of ordinary skill would need further experimentation in order to "identify functional siRNA." Applicants respectfully bring certain points to the examiner's attention, including that Applicants respectfully disagree with the Examiner's statement that the criteria have not been proven. As noted in Applicants' previous response, each individual criterion was determined and proven by bioinformatics techniques such as those described on pages 38 – 40 of the specification as filed, and although these criteria were established by bioinformatics techniques, patentability is not negated by the method of invention. 35 U.S.C. § 103 ("Patentability shall not be negatived by the manner in which the invention was made."). Further and as noted above, these claims are not directed to identifying functional siRNA – only siRNA with an increased likelihood of functionality. For the Examiner to reject claims 2 and 19 because they do not enable the selection of a functional siRNA is inappropriate. Because these claims are not specifically limited to the selection of an siRNA of a particular functionality, to require proof of the recital criteria ability to do so is inappropriate.

Applicants also submit that the Examiner is equating the proven set of criteria with the formulas that combine them. Although Applicants have proved that both the criteria individually and the formulas lead to an increase of the likelihood of functionality, it may be helpful to look at them separately. The individual criteria, *e.g.*, the presence or absence of a particular base at at least one of sequence positions 1 – 19, were proven through the bioinformatics techniques on pages 38 - 40. The formulas recited in claims 2 and 19 combine the proven sets of criteria with different weightings. Although Applicants submit that they are not required by the enablement requirement to demonstrate proof that the recited criteria increase the likelihood of functionality, Applicants submit that the bioinformatics techniques described in the application, adequately do demonstrate this point.

With these points in mind Applicants believe that the issue that the Examiner raises on page 4 may more easily be addressed.

As the specification teaches, because the invention as claimed in claim 2 is directed to a method for selecting siRNA based on criteria that increase the likelihood of functionality there may be instances when the siRNA that are suggested do not, when placed into an *in vitro* system have the desired level of functionality. However, the very passage cited by the Examiner teaches that in these circumstances a person of ordinary skill could simply try another one of the formulas. Thus, there is no undue experimentation or any experimentation in the selection process.

Third, in the two paragraphs that begin on page 5 and span to the top of page 6, the Examiner suggests that the specification is internally confusing because "if the SMARTscore method is be [*sic*] the best mode of operating the claimed method, then the formula or its method of practice should be disclosed in the specification as filed." This argument is a continuation of the argument from the prior Office Action that the specification is internally inconsistent because of the description of how to select hyperfunctional siRNA. Applicants respectfully traverse the Examiner's arguments.

As a threshold matter, Applicants' note that although section 112 of Title 35 requires disclosure of the best mode of practicing the invention, "[t]here is no requirement in 35 U.S.C. § 112 that an applicant point out which of his embodiments he considers his best mode." *Ernsthausen v. Nakayama,* 1 U.S.P.Q.2d 1539, 1549 (Bd. Pt. App. Int. 1986), *aff'd,* 809 F.2d 787 (Fed. Cir. 1986). Applicants respectfully submit that they have disclosed their best mode at the time of filing the application and thus, they are not required to disclose any more with respect to the selection of hyperfunctional siRNA of SMARTscore. For example, Applicants have disclosed the selection of hyperfunctional siRNA on page 53, line 4 – page 55, line 5 and page 155, line 19 – 29.

Further, through the disclosed formulas, Applicants have provided their best mode for selecting siRNA with an increased likelihood of functionality, and even the siRNA with the likelihood of the greatest functionality. For example, the specification specifically notes that when looking for hyperfunctional siRNA one can start with siRNA that have the highest SMARTscore. (Page 55, lines 21 –22 of the specification as application as filed.) However, Applicants did not suggest in the specification that the SMARTscore alone can be used to select hyperfunctional siRNA. They have only suggested that the use of SMARTscore is an appropriate starting point, and through additional steps that are both disclosed and well within the scope of the skill of a persons of ordinary skill in the art, a hyperfunctional siRNA can be identified.

Applicants also emphasize that except for claim 8, the rejection is inappropriate because an enablement rejection must be based on the whether the claims are enabled, and no claims other than claim 8 are directed to hyperfunctional siRNA. 35 U.S.C. § 112.

The Examiner extends her argument from hyperfunctional siRNA and asserts: "the skilled artisan is not given clear and specific guidance as how to use these particular criteria for rationally designing a functional or hyperfunctional siRNA." Applicants note that this argument appears inapplicable to rejected claims 1 – 6 and 19 – 34 because those claims are not directed to siRNA of a particular or absolute functionality, only with an increased likelihood of being functional or relative functionality. Thus, those claims

would be enabled even if the specification did not teach how to select a functional siRNA.

With respect to claims 35 – 37, Applicants submit that those claims, which are directed to selecting siRNA with functionalities of at least 70%, 85%, and 95%, respectively, are enabled. First, the specification teaches that the use of two of the recited formulas that generate SMARTscores of a certain level will give a functional siRNA. See page 40, lines 31-33. Thus, a person of ordinary skill would only need to apply one of those formulas to the potential siRNA for a target and select an siRNA with greater than the delineated SMARTscore. Further, the specification teaches to treat higher SMARTscores as suggestive of higher functionality. (Page 25, line 33 – page 26, line 1). Thus, a person of ordinary skill in the art could, for example, look for the highest SMARTscore when applying formulas VIII or IX to the set of siRNA for a target.

If for some reason this selection did not yield satisfactory results, the specification further notes (as the Examiner pointed out) that a person of ordinary skill in the art could turn to another formula. Alternatively, the person of ordinary skill could simply select the next highest SMARTscore. Further the specification teaches how to test empirically whether a selected siRNA has the desired functionality (see page 56 of application as filed). Thus, there is no undue experimentation necessary.

Based on the foregoing, Applicants respectfully submit that all of the pending claims satisfy the enablement requirement. If the Examiner disagrees, Applicants request that the Examiner identify specific claim limitations that she believes are not enabled.

Applicants also request that the Examiner clarify how the rejection is applicable to independent claim 6 and the claims that depend on it, claims 27 – 29.

Response to Rejection of claims 1 – 6, 8, 19 and 21 – 37

The Examiner rejects claim 1 – 6, 8, 19 and 21 – 37 as allegedly failing to comply with the written description requirement. Applicants respond as follows:

First, the Examiner states that the instant claims, other than claim 19 are not limited to those criteria recited in the specification. As a threshold matter, Applicants respectfully submit that this rejection is also inapplicable to claims 2 – 6 and 27 – 29. Claim 2 and the claims that depend on it (claims 3 –5) require the application of formulas that combine criteria that are specified in both the claims and the specification. (See *e.g.*, page 24, line 13 – page 25, line 2; page 28, line 1 – page 30, line 16.)

Independent claim 6 and the claims that depend on it (claims 27 – 29) are directed to methods for developing an algorithm, and it is unclear why they are lumped in with the other rejected claims as failing to comply with the written description requirement. Support for this method is found throughout the specification as filed, including, but not limited to, on page 12, lines 16 – 28 and page 30, line 34 – page 45, line 8. Thus, Applicants submit that it is unclear why this rejection was applied to those claims.

Second, the Examiner asserts that the Applicants' own specification suggests that other criteria not specifically disclosed are encompassed within the scope of the invention. She also asserts that there are many permutations to Formulas VIII and IX. However, it is unclear as to what other specific criteria the Examiner is referring. With respect to the cited passage on page 40, Applicants clarify the additional identified criteria as those elements include in Formulas VIII and IX. Further, the Examiner's concern with the permutations of the formulas is inappropriate. None of the claims are directed to permutations of the formulas. Claim 2 and the claims that depend on it are directed to methods that involve applications of the specified formulas, not the application of any of an infinite number of permutations of those formulas.

With respect to claim 1 and the claims that depend on it (while not depending on claim 2), Applicants submit that they have complied with the written description requirement. At the time of filing the invention Applicants had in their possession the inventive insight that by applying the claimed criteria *i.e.,* the presence or absence of a particular nucleotide at at least one of sequence positions 1-19 of the siRNA, they could increase or decrease the likelihood that a selected siRNA would be functional. The

specification amply demonstrates this. *See e.g.*, Table IV on page 40. Applicants also note that each of the elements of Formulas VIII and IX that are directed to weighting the presence or absence of a base at a particular position provides further support for the claims.

For example, if one focuses on Formulas VIII and IX, all positive weighted variables are examples of conditions that increase the likelihood of functionality while negatively weighted variables decrease the likelihood of functionality. Applicants have disclosed 37 parameters based on the presence or absence of a particular base at a particular position: A1, A2, A3, A4, A5, A6, A7, A10, A11, A13, A19, C3, C4, C5, C6, C7, C9, C17, C18, C19, G1, G2, G8, G10, G13, G19, U1, U2, U3, U4, U7, U9, U10, U15, U16, U17, and U18. (page 28, lines 30 – page 30, line 7 of the specification as filed) This more than amply demonstrates that at the time of filing the application, within scope of what Applicants believed was their invention and had in their possession was the use of the criterion of the presence or absence of a particular nucleotide at at least one of sequence positions 1-19 of the siRNA as a basis for increasing (or decreasing) the likelihood of functionality.

Third, the Examiner asserts that the claims lack a sufficient written description requirement regarding the application of a "proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." She cites pages 26, 40 – 41 and 53 and argues that there is ambiguity as to "which criteria would yield rationally designed siRNA." As noted above this argument suggests that Examiner is again equating rationally designed siRNA with siRNA of a specific functionality. As the claims and the specification clarify: "Rational design is, in simplest terms, the application of a proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." Page 21, lines 23 –25 of the specification as filed. Thus, the use of any of the 37 parameters alone or in combination is an example of an application of rationale design that would lead to an increased probability of selecting a functional siRNA.

The Examiner appears to suggest that there may be parameters other than the ones identified in the specification that exist, and because these may in theory exist, Applicants did not comply with the written description requirement. However, the written description requirement does not require an applicant to identify all possible non-specific criteria that depend on the presence or absence of the particular base at at least one of positions 1-19, only enough to demonstrate possession of the invention of using such criteria. *Kao Corp. v. Unilever,* 441 F.3d 963, 967 - 68 (Fed. Cir. 2006) (the disclosure as originally filed does not need to provide in *haec verba* support for the claimed subject matter); *Cordis Corp. v. Medtronic,* 339 F.3d 1352, 1365 (Fed. Cir. 2003) (an applicant is not required to describe in the specification every conceivable ad possible future embodiment of the invention). Applicants have identified 37 examples of such non-target specific criterion related to the presence or absence of a base at a particular position, and submit that this is more than sufficient to comply with the written description requirement.

With respect to claim 19, the Examiner expresses concern that there is no description with respect to the length of the sense strand. Applicants submit that the claim as amended obviates this rejection.

The Examiner's last sentence of the rejection reads: "it is unclear if the optimized siRNA represent functional or hyperfunctional siRNA." Applicants submit that this statement does not bear on compliance with the written description requirement. For the purpose of claim 19, whether the optimized siRNA is functional and also hyperfunctional does not come into play. All that is necessary is that the two siRNA that have the highest scores according to the any of the recited formulas are included a kit.

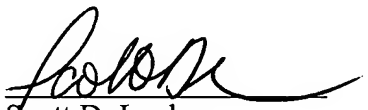
Conclusion

All of the Examiner's rejections having been fully traversed and addressed, Applicants respectfully request allowance of the pending claims.

Applicants submit that no fee is required in connection with the filing of this Amendment and Reply. If any fee is deemed necessary, please charge Deposit Account No. 11-0171.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,



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